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Platelet-derived growth factor receptor- expression in human peritoneum

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Abstract: INTRODUCTION: Simple peritoneal fibrosis and encapsulating peritoneal sclerosis (EPS) are important lesions in the peritoneum of patients on peritoneal dialysis (PD). We have previously described a population of podoplanin-positive myofibroblasts in peritoneal biopsies from patients with EPS. Platelet-derived growth factor receptor- (PDGFR) is a marker of pericytes, and PDGFs might be involved in the fibrotic response of the peritoneum. This study aimed to describe PDGFR in the human peritoneum. METHODS: In this retrospective analysis, we localized PDGFR in peritoneal biopsies from patients with EPS (n = 6) and patients on PD without signs of EPS (n = 5), and compared them with normal peritoneum (n = 4) and peritoneum from uremic patients (n = 5). Consecutive sections were stained for smooth-muscle actin (SMA) and podoplanin. Slides were scored semiquantitatively by 2 observers blinded to the diagnosis. RESULTS: PDGFR was expressed by cells of arterial walls in all biopsies. A prominent population of PDGFR -positive cells was present in the normal peritoneum, which were SMA negative on consecutive sections. In patients on PD, a high number of PDGFR were also positive for SMA. In EPS, the majority of podoplanin-positive cells were positive for PDGFR . In peritoneal biopsies from normal and uremic patients, the expression of SMA was mainly restricted to cells of arterial walls. Podoplanin expression was restricted to lymphatic vessels in normal peritoneum, in uremic patients, and in patients on PD without EPS. CONCLUSIONS: As podoplanin-positive myofibroblasts express PDGFR , these cells might be related to pericytes (rather than other sources of fibroblasts). PDGFR might turn out to be a therapeutic target in EPS. © 2014 S. Karger AG, Basel.

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Platelet-Derived Growth Factor Receptor-β Expression in Human Peritoneum

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Key Words
Platelet-derived growth factor receptor-β · Podoplanin · Encapsulating peritoneal sclerosis · Lymphatic vessels

Abstract
Introduction: Simple peritoneal fibrosis and encapsulating peritoneal sclerosis (EPS) are important lesions in the peritoneum of patients on peritoneal dialysis (PD). We have previously described a population of podoplanin-positive myofibroblasts in peritoneal biopsies from patients with EPS. Platelet-derived growth factor receptor-β (PDGFRβ) is a marker of pericytes, and PDGFs might be involved in the fibrotic response of the peritoneum. This study aimed to describe PDGFRβ in the human peritoneum. ***Methods:*** In this retrospective analysis, we localized PDGFRβ in peritoneal biopsies from patients with EPS (n = 6) and patients on PD without signs of EPS (n = 5), and compared them with normal peritoneum (n = 4) and peritoneum from uremic patients (n = 5). Consecutive sections were stained for smooth-muscle actin (SMA) and podoplanin. Slides were scored semiquantitatively by 2 observers blinded to the diagnosis. ***Results:*** PDGFRβ was expressed by cells of arterial walls in all biopsies. A prominent population of PDGFRβ-positive cells was present in the normal peritoneum, which were SMA negative on consecutive sections. In patients on PD, a high number of PDGFRβ were also positive for SMA. In EPS, the majority of podoplanin-positive cells were positive for PDGFRβ. In peritoneal biopsies from normal and uremic patients, the expression of SMA was mainly restricted to cells of arterial walls. Podoplanin expression was restricted to lymphatic vessels in normal peritoneum, in uremic patients, and in patients on PD without EPS. ***Conclusions:*** As podoplanin-positive myofibroblasts express PDGFRβ, these cells might be related to pericytes (rather than other sources of fibroblasts). PDGFRβ might turn out to be a therapeutic target in EPS.

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Introduction

Simple peritoneal fibrosis and encapsulating peritoneal sclerosis (EPS) are important consequences of long-term peritoneal dialysis (PD) with major impact

H.S. and N.B. contributed equally to this work.

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on technical and patient survival [1, 2]. We have previously described a population of podoplanin-positive cells in peritoneal biopsies from patients with EPS [3, 4]. These cells coexpress smooth-muscle actin (SMA; a marker of myofibroblasts) and podoplanin. Under normal conditions, podoplanin is expressed by lymphatic endothelial cells and mesothelial cells in the peritoneum. We demonstrated that 15 of 18 biopsies from patients with EPS demonstrated a diffuse accumulation of podoplanin-positive cells [3], whereas these cells were focally present in 3 of 16 specimens from PD patients without signs of EPS, and in none of the 35 controls [3]. Podoplanin-positive cells appear in four morphological patterns [4]. An organized pattern was found in 8 of 24 biopsies, with longitudinal layers of podoplanin-positive cells, a diffuse pattern (in 7 of 24 biopsies) with a random and at times dense podoplanin-positive cell accumulation, and a combination of those two patterns ('mixed' in 5 of 24 biopsies) [4]. As in the previous study, in biopsies of some patients, an accumulation of podoplanin-positive myofibroblasts was not present, but only expression by lymphatic endothelial cells (4 of 24 biopsies, podoplanin 'low') [4]. The diffuse and mixed patterns were associated with higher C-reactive protein levels (as a marker of systemic inflammation) and a shorter time between onset of symptoms and EPS diagnosis [4].

Platelet-derived growth factors (PDGFs) and their receptors (PDGFRs) play pivotal roles in driving fibroblast and vascular smooth muscle cell proliferation, as well as production of extracellular matrix [5]. The two PDGF receptor chains (PDGFRα and PDGFRβ) form homodimers and heterodimers. The receptors containing the β-chains (PDGFRαβ and PDGFRββ) bind the ligands PDGF AB or BB, and PDGF BB or DD, respectively [5, 6].

Pericytes are mesenchymal-derived cells which have been described to be a major source for fibroblasts in renal injury models [7, 8] as well as in other organs [9]. Within the renal tubulointerstitium, the majority of SMA-positive cells were derived from pericytes, which expressed PDGFRβ [10]. Several previous studies used PDGFRβ to describe the distribution of pericytes, and therefore it is an accepted marker of pericytes [11–13]. The corresponding ligand PDGF B is an important differentiation factor for pericytes [14]. As the source of myofibroblasts in the peritoneal cavity is still poorly described, this study aimed to further characterize the expression of the PDGFRβ in the human peritoneum and by doing so to elucidate pericytes as a potential source of podoplanin-positive myofibroblasts.

Materials and Methods

In this retrospective analysis, we included peritoneal biopsies from patients with EPS (n = 6) and patients on PD without signs of EPS (n = 5), and compared them with normal peritoneum (n = 3) and peritoneum from uremic patients (n = 5). Consecutive sections were stained for PDGFRβ (Y92, EPITOMICS, Burlingame, Calif., USA), SMA (1A4, DakoCytomation, Glostrup, Denmark), and podoplanin (D2–40, Signet Laboratories, Dedham, Mass., USA) as previously described in detail [3, 4]. Slides were scored semiquantitatively by 2 observers blinded to the diagnosis. The interobserver variability of the scores reflected by weighted κ were 0.61 for PDGFRβ, 0.68 for podoplanin and 0.56 for SMA. Illustrated were the mean of the two scores ± SEM.

The tissue sections were obtained from the peritoneal biopsy registry at the Robert-Bosch-Hospital, Stuttgart, Germany. The collection of human peritoneal tissue, blood and peritoneal dialysate for research purposes was approved by the local ethics committee (#322/2009BO1, Eberhard-Karls University Tübingen, Germany). All patients had given their written informed consent concerning a scientific workup of tissues taken during surgery.

Biopsies from the peritoneum from EPS patients were obtained during peritonectomy and enterolysis. These were formalin-fixed and paraffin-embedded following routine protocols. The clinical information is illustrated in table 1. For the diagnosis of EPS, the clinical criteria described by Nakamoto [15], radiological criteria by Vlijm et al. [16] and histological criteria by Honda et al. [17] were applied. The morphological features of podoplanin staining were used as previously described [4].

Statistics

The nonparametric Kruskal-Wallis was performed with Dunn's multiple comparison (posttest) for the comparison of immunohistochemistry scores using Graph Pad Prism 5 for Windows (version 5.03). A $p < 0.05$ was considered statistically significant. Illustrated in the scatterplots are mean ± SEM. The interobserver variability was illustrated by calculating weighted κ (using Graphpad Quickcalcs online software at http://graphpad.com/quickcalcs/kappa1.cfm).

Results

Localization of PDGFRβ in Peritoneal Biopsies

The clinical information of the studied patients is summarized in table 1. As the control groups were small, these were combined in the further analysis (3 biopsies with normal peritoneum and 5 from uremic patients). Looking at the results of the uremic patients separately did not change the results.

PDGFRβ was expressed by cells of arterial walls in all biopsies as expected (fig. 1a). In the biopsies with well-preserved peritoneum, a number of PDGFRβ-positive cells was scattered throughout the interstitial tissue particularly in the vicinity of larger arteries. These PDGFRβ-positive interstitial cells with the appearance of fibroblasts were not positive for SMA or podoplanin on con-

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Table 1. Clinical information and laboratory values of study population (n or mean ± SD)

Variable	Normal biopsies	Uremic patients (not on PD)	PD	EPS
Patients	3	5	5	6
Female/male	2/1	3/2	4/1	5/1
Age, years	50.2±13.2	54.4±18.1	64.4±11.8	51.3±9.9
PD duration, months			24.2±19.1	70.5±22.3
Peritonitis rate, months			1:15	1:47
PDF				
Neutral			4	2
Acidic			0	3
ND			1	1
Icodextrin			2/5	5/6
Transporter status				
High/high average			2	4
Low/low average			1	
ND			2	2
Diabetes	0/3	3/5	3/5	0/6
Smoker	0/3	2/5	2/5	2/6
Hypertension	1/2	3/5	4/5	6/6
Laboratory values				
Hb, g/dl (13–18)	12.9±2.4	10.6±1.0	12.3±2.2	10.0±1.8
Leukocytes, g/l (4.0–11.3)	4.8±1.0	8.5±1.7	6.4±1.6	6.9±3.2
Phosphate, mmol/l (0.68–1.68)		1.7±0.3	1.3±0.4	1.1±0.3
Calcium, mmol/l (1.90–2.70)	2.3±0.1	2.1±0.1	2.2±0.1	2.1±0.2
PTH, pmol/l (1.1–7.3)		34.3±8.3	31.1±29	37.2±47.1
Urea-N, mg/dl (10–25)		65.6±23.5	44.6±22.5	37.8±15.3
Creatinine, mg/dl (0.5–1.4)	0.8±0.1	5.1±1.0	5.1±2.6	6.9±3.7

PDF = Peritoneal dialysis fluid; Hb = hemoglobin; ND = not determined; PTH = parathyroid hormone. Figures in parentheses indicate normal ranges.

secutive sections. SMA was almost exclusively restricted to arterial walls. Therefore, a population of scattered PDGFRβ-positive cells with fibroblastic appearance was found to be SMA negative. In the control biopsies, podoplanin was restricted to mesothelial cells and lymphatic vessels. The semiquantitative scores for PDGFRβ-positive cells were higher than for SMA-positive cells in normal peritoneum (due to the described population; fig. 2).

In the 5 biopsies from patients on PD without EPS, a prominent accumulation of PDGFRβ-positive cells was present particularly in the submesothelial fibrotic area (fig. 1d–f). An overlapping pattern was seen in these fibrotic areas for SMA. Still, the number of PDGFRβ-positive cells outnumbered the SMA-positive cells in many areas (fig. 1d, f). This indicates that at least two populations of PDGFRβ are present in the injured peritoneum (the double-positive cells reflect myofibroblasts). Importantly there was also a strong and diffuse accumulation of SMA and PDGFRβ-positive cells; no podoplanin staining was present on consecutive sections (fig. 1e). Therefore, myofibroblasts in simple fibrosis related to PD do not express podoplanin.

Five of the 6 biopsies from patients with EPS demonstrated a diffuse accumulation of podoplanin-positive cells (fig. 1g–i). Both the PDGFRβ and the SMA staining demonstrated a very similar pattern. Therefore, in EPS a third population of cells was present expressing all three markers. In EPS, the three markers labelled the same fibroblastic cells, but differed in the labelling of vessel walls and lymphatic vessels (as expected). A significant increase in the PDGFRβ, SMA, and podoplanin scores was seen in EPS as compared to controls (fig. 2).

Discussion

Pericytes found major attention as the source for the extracellular matrix producing myofibroblasts [13]. Pericytes are located on the abluminal surface of small vessels,

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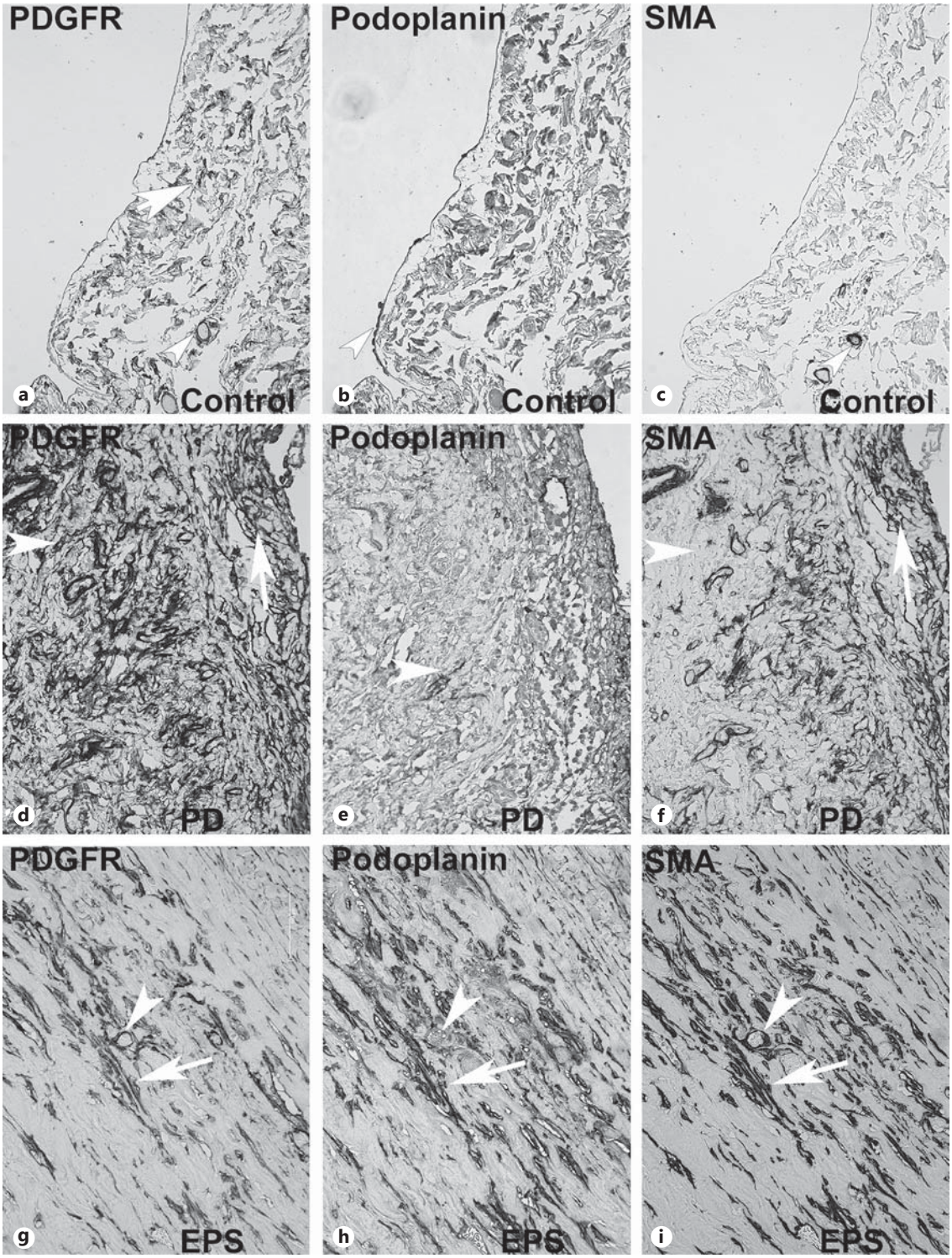

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and are embedded in part in the vascular basement membrane [13]. In several organs including the liver, kidney and skin in systemic sclerosis, the pericyte has been suggested as a major source of myofibroblasts [reviewed in 13]. Furthermore, pericytes play a role in angiogenesis [18]. The distribution of pericytes in the peritoneum from patients on PD has not been illustrated. Furthermore, the source of myofibroblasts during peritoneal injury has not been well defined. Postulated sources are a tissue-resident cell (like a pericyte), bone marrow-derived cells (fibrocytes), cells derived from the epithelium (epithelial-mesenchymal transition, EMT), as well as from endothelial cells [9]. EMT has been given a lot of attention in peritoneal fibrosis as in renal fibrosis [2, 19]. In renal fibrosis, the enthusiasm for EMT as a major contributor to myofibroblasts has decreased as genetic tracing experiments were not consistent with this mechanism [20]. A recent study used cell fate mapping in models of peritoneal injury. It did not find evidence for EMT but described a population of fibroblasts consistent with pericytes as the source of myofibroblasts [21].

To further define the source and potential mechanism of peritoneal fibrosis, this retrospective analysis was performed in the human peritoneum. In the normal peritoneum, a scattered population of PDGFRβ-positive cells with fibroblastic appearance was present which did not express SMA. In patients on PD, a high number of PDGFRβ-positive cells were present. On consecutive sections, a larger population of these cells colocalized with SMA-positive cells and therefore reflects myofibroblasts. These cells did not express podoplanin. In EPS, the podoplanin-positive cell population demonstrated an overlapping pattern for both SMA and PDGFRβ. Therefore, this is the first study which illustrates three different populations of cells with fibroblastic appearance in the human peritoneum. The scattered PDGFRβ-positive cells (which neither express podoplanin nor SMA) in the normal peritoneum most likely reflect pericytes. Two populations of myofibroblasts are present in peritoneal fibrosis and EPS. These can be separated by the expression of podoplanin. All three markers come together in EPS. The expression of PDGFRβ suggests that the myofibroblasts in perito-

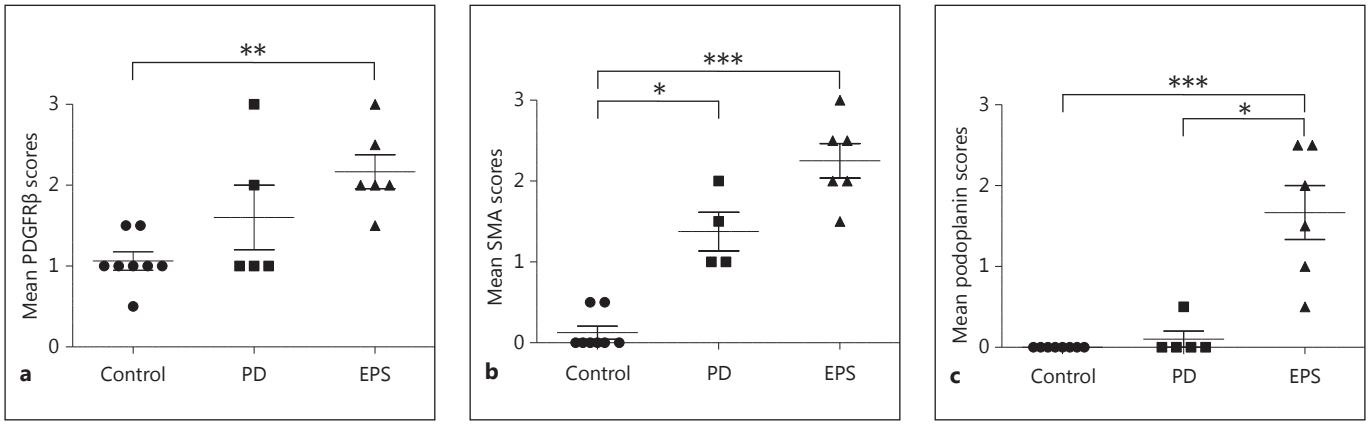

Fig. 2. Illustration of the expression of PDGFRβ, SMA and podoplanin in peritoneal biopsies. Mean semiquantitative scores are illustrated as scatter plots. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Fig. 1. Illustration of PDGFRβ in peritoneal biopsies. Immunohistochemistry was performed on consecutive tissue sections from peritoneal biopsies of patients not on PD (**a–c**), on PD without signs of EPS (**d–f**) and on PD with signs of EPS (**g–i**) for PDGFRβ (**a**, **d**, **g**), podoplanin (**b**, **e**, **h**), and smooth muscle actin (SMA; **c**, **f**, **i**). In normal peritoneal biopsies, PDGFRβ was found to be expressed in the vessel walls of larger and smaller arteries (as expected for pericytes; arrowhead in **a**); additionally, a prominent population of interstitial cells with fibroblastic appearance was positive (arrow in **a**). Podoplanin was expressed by mesothelial cells (arrowhead in **b**) and SMA in smooth muscle cells of arteries and arterioles (arrowhead in **c**). A prominent consecutive accumulation of PDGFRβ-positive cells and SMA-positive cells was present in the submesothelial fibrotic zone in the patient on PD (arrowhead in **d** and **f**). In contrast, PDGFRβ-positive cells outnumbered the SMA-positive cells in some areas (arrow in **d** and **f**). The podoplanin staining demonstrates only scattered lymphatic vessels (arrowhead in **e**). In EPS, the podoplanin-positive cell population (arrow in **g**–**i**) demonstrated expression of all three markers, whereas no overlap was seen in the vascular cells (arrowhead in **g–i**).

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neal injury are related to pericytes. These data are consistent with a recent study which demonstrated that the majority of myofibroblasts in mice after peritoneal injury come from a local population of fibroblasts [21]. Furthermore, these cells expressed PDGFRβ [21].

PDGFRβ might not only be a marker, but also a functional player in both peritoneal fibrosis and EPS. This receptor binds PDGF AB, PDGF BB or DD (depending on the second PDGFR chain).

In vitro, it has been demonstrated that PDGF-AB resulted in a time- and dose-dependent proliferation of human peritoneal fibroblasts [22]. Peritoneal dialysate from patients with peritonitis induced proliferation of these cells, which could be partially inhibited by an anti-PDGF antibody [22]. Overexpression of PDGF-B in the peritoneum resulted in angiogenesis, increased collagen gene expression, but only transient fibrogenesis [23, 24]. Imatinib mesylate is a tyrosine kinase inhibitor which inhibits PDGFR signaling and is increasingly used for fibrotic diseases like systemic sclerosis [25], nephrogenic systemic fibrosis [26] and others. Imatinib has been used in the model of chlorhexidine-induced peritoneal injury in rats without a significant effect on peritoneal fibrosis [27]. In contrast, in a model of hypochlorite-induced peritoneal injury, imatinib reduced fibrosis [21]. An important piece of information from the study is that the podoplanin-positive myofibroblasts in EPS also express PDGFRβ. Ascites from patients with EPS contained elevated levels of PDGF-AB and induced proliferation of fibroblasts in vitro [28]. Furthermore, proliferation of fibroblasts was partially blocked by a tyrosine kinase inhibitor [28]. This not only implies pericytes as a potential source of this cell population, and PDGF-B as a potential pathogenic factor, but it also provides a therapeutic target.

This retrospective analysis has shortcomings. Most importantly, only a small number of biopsies was included in this analysis. Unfortunately, we have no information on the levels of PDGF AB, BB or DD in the dialysate of these patients. Finally, a general problem is that there is no single marker for pericytes. Therefore, pericytes need to be defined by the combination of ultrastructural analysis and two or more markers of pericytes [e.g. PDGFRβ, chondroitin sulfate proteoglycan 4 (NG2), SMA, etc]. Multicolor fluorescence will help in future studies to further define these cells in the peritoneum. Due to restrictions of materials and antibodies which work on archival tissue, we were limited to consecutive sections in the current study.

We suggest that PDGFRβ-positive cells might play an important role in human peritoneal injury, and therefore the pathogenetic role of these cells (pericytes as a source of fibroblasts) and targeting these cells need to be further evaluated.

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Disclosure Statement

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